modification results in the absence of expression of at least one *CASP8* allele and reduction in the total level of expression of CASP8 protein to below that necessary for proper cellular regulation.

56. (New) A method for detecting inactivation of a *CASP8* gene, comprising detecting a methylation of genomic DNA comprising the *CASP8* gene promoter.

57. (New) The method according to claim 56, wherein methylation of the *CASP8* promoter is detected by methylation polymerase chain reaction (PCR) assay.

REMARKS

Applicants have carefully studied the Office Action mailed on October 24, 2001, which issued in connection with the above-identified application. The present amendments and remarks are intended to be fully responsive to all points of rejection raised by the Examiner and are believed to place the claims in condition for allowance. Favorable reconsideration and allowance of the present claims are respectfully requested.

Pending Claims

Claims 1-47 were pending and at issue in the application. In the Office Action, the Examiner made final the election of claims 1-20 and 26-29 and withdrew claims 21-25 and 30-47 from consideration. Applicants note gratefully that the Examiner has withdrawn the species requirement and examined claims both with respect to nucleic acids and proteins.

Claims 10-20 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1-10, 13-20, and 26-29 have been rejected under 35 U.S.C. § 102 and/or under 35 U.S.C. § 103(a) as being anticipated by or obvious over the prior art.

Claims 1, 10, and 26 have been canceled. Claims 2, 4, 6, 11-13, 15, 17, and 27-29 have been amended to correct dependency. New claims 48-57 have been added in order to more particularly point out and distinctly claim the invention. New claims 48, 51, and 55 are directed to the subject matter of canceled claims 1, 10, and 26, respectively. Accordingly, these new claims find support in the respective original claims. Specific support for the recitation "[*CASP8*] modification results in the absence of expression of at least one *CASP8* allele and reduction in the total level of expression of CASP8 protein to below that necessary for proper cellular regulation" in claims 48, 51, and 55 can be found, for example, at page 7, lines 15-20; page 8, lines 13-20; page 30, lines 10-11, and Example 2 (pages 48-51) of the present specification. Note that these new claims expressly recite features implicit to the claims as filed, since these claims merely recite the definitions of "inactivation", "poor prognosis" and other terms in the specification. Accordingly, the new claims are of the same scope as the claims as filed. Support for the recitation "for outcome of treatment of the cancer by conventional therapies" in claim 51 can be found, for example, at page 3, lines 8-9. Specific support for new claims 49, 50, 52, and 53 can be found, for example, at page 30, lines 22-26. Specific support for new claim 54 can be found, for example, at page 7, lines 15-17. Support for new claims 56 and 57 can be found, for example, in the original claims 4 and 15; in Example 3 (pages 51-57); at page 3, lines 27-28; page 29, line 24 - page 30, line 7, and in Figures 6A, 6B, and 7A. No new subject matter has been added as a result of these amendments; no new search is required, and no new issues are raised. Upon entry of these amendments, claims 2-9, 11-20, 27-29, and 48-57 will be pending.

35 U.S.C. § 112, Second Paragraph, Rejections

In the Action, the independent claim 10 and its dependent claims 11-20 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner states that the term "poor prognosis" in claim 10 is a relative term, which is not defined by the claims or by the specification.

As claim 10 has been canceled, the rejection of this claim is rendered moot. The remaining rejected claims 11-20 have been amended to depend from new claim 51. The rejection with respect to these claims is respectfully traversed. It is respectfully submitted that, in contrast to the Examiner's assertion, the term "poor prognosis" is well understood in the art to mean, simply, that the person is less likely than others to get well. Moreover, at page 3, lines 8-9 of the instant application it is specifically defined that the term "poor prognosis" means "poor prognosis for outcome of treatment of the cancer, at least by conventional therapies." In the interest of expediting allowance of the present application, new claim 51 recites the express definition from the specification.

In light of the foregoing, applicants respectfully submit that the rejection of the claims based upon 35 U.S.C. §112, second paragraph, is overcome and withdrawal of such is kindly requested.

35 U.S.C. § 102(b) Rejection

In the Office Action, claims 1, 6-8, and 17-19 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Mandruzzato *et al.*, J. Exp. Med., 186: 785-793, 1997 (hereinafter "Mandruzzato *et al.*"). The Examiner contends that this reference anticipates claims because it teaches a method of diagnosis or prognosis of cancer by detecting inactivation of a

CASP8 gene, said method comprising detecting a modification of *CASP8* genomic DNA. The Examiner further states that the mutations detected by Mandruzzato *et al.* include a deletion.

As claim 1 has been canceled, the rejection of this claim is rendered moot.

The remaining rejected claims 6-8 and 17-19 have been amended to depend from new claims 48 and 51, respectively.

Claims 48 and 51 recite that the gene-inactivating modification of the *CASP8* gene associated with cancer results in the absence of expression of at least one *CASP8* allele and reduction in the total level of expression of CASP8 protein to below that necessary for proper cellular regulation. In contrast to the present invention, Mandruzzato *et al.* do not disclose or suggest that inactivation of *CASP8* gene in cancer results from the absence of expression of one or both *CASP8* alleles. In the squamous cell carcinoma cell line described in this article, both *CASP8* alleles are expressed. One allele expresses a wild-type CASP8 protein, and the other allele expresses a mutated CASP8 protein with 88 extra residues at the C-terminus. Thus, as stated at page 790 (right column, paragraph 4), "[t]he tumor cells of patient BB49 express both a normal and a mutated allele of *CASP-8*" (emphasis added). The mutated *CASP8* allele discovered by Mandruzzato *et al.* produces a mutated protein, which is partially functional in apoptosis. Indeed, as stated at page 791 of the article (left column, paragraph 2), "when the mutated CASP-8 gene was transiently transfected in 293-EBNA cells: its ability to trigger apoptosis was reduced relative to the normal caspase-8 but not abolished" (emphasis added). As authors further discuss at page 790 (right column, paragraph 4): "Assuming that caspase-8 adopts a conformation similar to the p20/p10 tetramer of caspase-1, the mutation may decrease the activity of the enzyme because the active tetramer cannot be assembled with the abnormal p19 subunits. Moreover, the p19 subunit may impede the folding of the tetramers containing subunits of the normal caspase-8, thereby resulting in a partially dominant effect." In contrast, the present invention relates to the discovery that cancers associate with a mutated *CASP8* allele

that produces no protein and therefore is neither able to partially fulfill the function of the wild-type protein nor to inhibit it (*e.g.*, by forming non-functional oligomers).

Mandruzzato *et al.* state at page 791 (right column, first paragraph) that "it is likely that the mutation in the stop codon is not the only one to be deleterious to the activity of caspase-8. Mutations in other critical parts of the protein, such as the different cleavage sites, the catalytic site, or the domain that interacts with FADD, may be observed in other tumors." It follows, that, although Mandruzzato *et al.* could envision the possibility of other cancer-associated mutations in the *CASP8* coding sequence resulting in the production of mutant proteins, they did not anticipate that the absence of CASP8 protein expression from at least one of the alleles may also associate with cancer. This difference between Mandruzzato *et al.* reference and the present application, is particularly evident from the absence of any disclosure or suggestion in Mandruzzato *et al.* of the modifications in the non-coding regions of the *CASP8* gene, such as the promoter region. At page 7 of the Office Action (paragraph 4), the Examiner affirms this conclusion by stating that "Mandruzzato *et al.* fails to teach detection of the ... methylation of *CASP8* promoter..."

For the record, applicants would also like to note that the Examiner's statement that the *CASP8* mutations detected by Mandruzzato *et al.* include a deletion is believed to be incorrect. As specified above (and disclosed in the Abstract of the article and at pages 789-790 as correctly stated by the Examiner), the only *CASP8* mutation described by Mandruzzato *et al.* is a single nucleotide change (*i.e.*, a point mutation) within the *CASP8* coding sequence, which eliminates the stop codon, increasing the size of the encoded CASP8 protein by 88 amino acids.

In view of the arguments and amendments presented above, applicants respectfully submit that the rejected claims 6-8 and 17-19 as well as new claims are not anticipated by Mandruzzato *et al.* article. Reconsideration and withdrawal of the anticipation rejection is believed to be in order.

35 U.S.C. § 102(e) Rejection

In the Office Action, claims 1-3, 6-10, 13-14, 17-20, and 26-29 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,172, 190 by Hunter *et al.* (hereinafter "the '190 patent"). The Examiner contends that the '190 patent anticipates these claims because it teaches a method of diagnosis or prognosis of a disorder associated with apoptotic cell death by detecting inactivation of the *CASP8* gene by detecting modification of the *CASP8* genomic DNA (including deletions). The Examiner also states that the '190 patent teaches detecting the *CASP8* gene inactivation using such methods as (i) immunoassay to detect the lack of CASP8 protein and (ii) labeled nucleotide probes or PCR primers to detect the modification of *CASP8* DNA.

As claims 1, 10, and 26 have been canceled, the rejection of these claims is rendered moot.

The remaining rejected claims have been amended to depend from new claims 48, 51, or 55.

Claims 48, 51, and 55 recite that the gene-inactivating modification of the *CASP8* gene associated with cancer results in the absence of expression of at least one *CASP8* allele and reduction in the total level of expression of CASP8 protein to below that necessary for proper cellular regulation. In contrast to the present invention, the '190 patent does not disclose or suggest that the improper function of *CASP8* gene in apoptosis can be associated with the absence of expression of one or both *CASP8* alleles. In fact, this patent does not discuss at all the issue of how *CASP8* can be inactivated in cancer. The '190 patent is directed to two novel truncated forms of CASP8 protein: Caspase-8h, which encodes a 220 amino acid polypeptide and includes two FADD death effector domains, and Caspase-8i, which encodes an 81 amino acid polypeptide and has only one FADD death effector domain. As specified above, the present

invention relates to the discovery that cancers associate with a mutated *CASP8* allele that produces no protein and is neither able to partially fulfill the function of the wild-type protein nor to inhibit it. . In contrast, mutant CASP8 proteins disclosed the '190 patent are expressed, exert biochemical function, and affect CASP8-mediated apoptosis signaling cascade. As disclosed, for example, in column 4, lines 3-10: "[b]ecause Caspase-8h and Caspase-8i lack the ICE/CED-3 domain that is required for carrying out apoptosis, but have FADD death effector domains required for interaction with Fas/APO-1, they may compete with other forms of Caspase-8 for binding to the Fas/APO-1 complex. Accordingly, increased expression of Caspase-8h and/or Caspase[0]8i may decrease Fas/APO-1 mediated apoptosis (or TNF receptor mediated apoptosis)" (emphasis added).

In contrast to the present invention and contrary to the Examiner's assertion, although the '190 patent describes that oligonucleotide probes and PCR primers can be used for the identification of gene mutations[1], it does not disclose or suggest that labeled oligonucleotide probes or PCR primers can be used to detect *CASP8*-inactivating mutations resulting in the absence of expression of at least one *CASP8* allele. For example, the '190 patent does not disclose or suggest any methods for detecting *CASP8* promoter methylation.

Accordingly, applicants respectfully submit that the new claims and rejected claims 2-3, 6-9, 13-14, 17-20, and 27-29 are not anticipated by the '190 patent. Reconsideration and withdrawal of the anticipation rejection is believed to be in order.

35 U.S.C. § 103(a) Rejections

In the Action, claims 1-3, 6-10, 13-14, 17-20, and 26-29 stand rejected under 35 U.S.C. § 103(a) as being obvious over Mandruzzato *et al.* in view of the '190 patent or PCT

[1] *See, e.g.*, column 5, lines 27-30.

Application No. WO 97/46662 by Dixit *et al.* (hereinafter "WO 97/46662"). The Examiner contends that both Mandruzzato *et al.* and the '190 patent teach a method of diagnosis or prognosis of cancer by detecting inactivation of a *CASP8* gene, said method comprising detecting a modification of *CASP8* genomic DNA. The Examiner further notes that both the '190 patent and WO 97/46662 also teach detecting gene mutation using such methods as (i) immunoassay to detect a lack of protein and (ii) labeled nucleotide probes or PCR primers to detect the modification of DNA. The Examiner concludes that, at the time the invention was made, it would have been obvious to one of ordinary skill in the art to use the methods of determination of gene inactivation taught by the '190 patent and WO 97/46662, to detect *CASP8* gene modifications taught by Mandruzzato *et al.*

As claims 1, 10, and 26 have been canceled, the rejection of these claims is rendered moot.

The remaining rejected claims have been amended to depend from new claims 48, 51, or 55.

Claims 48, 51, and 55 recite that the gene-inactivating modification of the *CASP8* gene associated with cancer results in the absence of expression of at least one *CASP8* allele and reduction in the total level of expression of CASP8 protein to below that necessary for proper cellular regulation. According to the present invention, cancers associate with a mutated *CASP8* allele that produces no protein and therefore is neither able to partially fulfill the function of the wild-type protein nor to inhibit it.

As specified above, in contrast to the present invention, neither Mandruzzato *et al.* nor the '190 patent disclose or suggest that inactivation of *CASP8* gene in cancer results from the absence of expression of one or both *CASP8* alleles. In the squamous cell carcinoma cell line described in Mandruzzato *et al.*, both *CASP8* alleles are expressed. One allele expresses a wild-type CASP8 protein, and the other allele expresses a mutated CASP8 protein (with 88 extra

residues at the C-terminus), which is partially functional in apoptosis. The '190 patent discloses two novel truncated forms of CASP8 protein, Caspase-8h and Caspase-8i, which are able to compete with the wild-type CASP8 for the interactions with other molecules in the apoptosis signaling cascade.

In contrast to the Examiner's assertion, it is respectfully submitted that, although the '190 patent describes that oligonucleotide probes and PCR primers can be used for the identification of gene mutations, it does not disclose or suggest that these reagents can be used to detect *CASP8*-inactivating mutations resulting in the absence of expression of at least one *CASP8* allele. Thus, the '190 patent does not disclose or suggest any methods for detecting *CASP8* promoter methylation.

WO 97/46662 does not disclose *CASP8*. Similarly to the '190 patent, it also does not disclose or suggest that labeled oligonucleotide probes and PCR primers can be used to detect gene-inactivating mutations resulting in the absence of expression of at least one allele.

Accordingly, applicants respectfully submit that, even if taken together, Mandruzzato *et al.*, the '190 patent, and WO 97/46662 do not disclose or suggest the methods and kits encompassed by the present claims. It follows, that the new claims and rejected claims 2-3, 6-9, 13-14, 17-20, and 27-29 are not obvious over the cited art. Reconsideration and withdrawal of the obviousness rejection is believed to be in order.

In the Office Action, claims 1, 4-6, and 15-17 have been further rejected under 35 U.S.C. § 103(a) as being obvious over Mandruzzato *et al.* in view of Herman *et al.*, Proc. Natl. Acad. Sci. USA, 93: 9821-9826, 1996 (hereinafter "Herman *et al.* (1)") or Herman *et al.*, Proc. Natl. Acad. Sci. USA, 91: 9700-9704, 1994 (hereinafter "Herman *et al.* (2)"). The Examiner contends that Mandruzzato *et al.* teach a method of diagnosis or prognosis of a cancer by detecting inactivation of a *CASP8* gene, said method comprising detecting a modification of *CASP8* genomic DNA. The Examiner further notes that (i) both Herman *et al.* (1) and Herman

et al. (2) teach that aberrant promoter methylation is a common mutation in tumor suppressor genes in human cancers, and (ii) Herman *et al.* (1) also teaches the use of methylation-sensitive PCR. The Examiner concludes that Mandruzzato *et al.* article discloses that other mutations of *CASP8* are helpful in tumor studies and in this way provides a motivation for one of ordinary skill in the art to detect *CASP8* promoter methylation using the methods of Herman *et al.*

Similarly, claims 1-10, 13-20, and 26-29 stand rejected under 35 U.S.C. § 103(a) as being obvious over Mandruzzato *et al.* in view of the '190 patent or WO 97/46662, and further in view of Herman *et al.* (1 or 2). The Examiner again states that Mandruzzato *et al.* article discloses that other mutations of *CASP8* are helpful in tumor studies and in this way provides a motivation for one of ordinary skill in the art to use the methods for determination of gene inactivation taught in the '190 patent and WO 97/46662, or to detect *CASP8* promoter methylation using the methods of Herman *et al.*

As claims 1, 10, and 26 have been canceled, the rejection of these claims is rendered moot.

The remaining rejected claims have been amended to depend from new claims 48, 51, or 55.

The rejection is respectfully traversed. It is respectfully submitted that, contrary to the Examiner's assertion, neither alone nor together do Mandruzzato *et al.*, the '190 patent, and WO 97/46662 disclose or suggest (i) that inactivation of *CASP8* gene in cancer can be caused by methylation of its promoter DNA (or any other mutation resulting in the absence of expression of at least one *CASP8* allele), or (ii) that labeled oligonucleotide probes or PCR primers can be used for the detection of *CASP8* promoter methylation.

The only *CASP8* mutation described in Mandruzzato *et al.* is a single nucleotide change (*i.e.*, a point mutation) within the *CASP8* coding sequence, which eliminates the stop codon increasing the size of the encoded CASP8 protein by 88 amino acids. As noted by the

Examiner (page 7, paragraph 4 of the Office Action), "Mandruzzato *et al.* fails to teach detection of the ... methylation of *CASP8* promoter, using polymerase chain reaction (PCR) assay." Applicants respectfully submit that the Examiner's position that Mandruzzato *et al.* article discloses that other mutations of *CASP8* are helpful in tumor studies and in this way provides a motivation for one of ordinary skill in the art to detect *CASP8* promoter methylation using the methods of Herman *et al.*, is incorrect. On the contrary, Mandruzzato *et al.* teach away from detecting DNA modifications in the non-coding regions of the *CASP8* gene (*e.g.*, promoter) by emphasizing the importance of mutations in the coding region (*see* the citation provided above [page 791, right column, first paragraph]). Accordingly, in contrast to the Examiner's assertion, Mandruzzato *et al.* article does not provide any guidance or motivation to detect *CASP8* promoter methylation.

As explained in detail above, the '190 patent also does not disclose or suggest detecting methylation of *CASP8* gene promoter or any other mutation resulting in the absence of expression of at least one *CASP8* allele. WO 97/46662 does not disclose *CASP8* or any methods for detecting promoter methylation.

It follows that, based on the disclosure of Mandruzzato *et al.* (even if taken together with the '190 patent, and WO 97/46662) a person of ordinary skill in the art would not be motivated to apply the method of Herman *et al.* (*i.e.*, methylation-sensitive PCR) to detect a DNA modification leading to the inactivation of the *CASP8* gene.

In view of the arguments and amendments presented above, applicants respectfully submit that the rejected and new claims are not obvious over the cited art. Reconsideration and withdrawal of the obviousness rejection is believed to be in order.

CONCLUSION

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that claims 2-9, 11-20, 27-29, and 48-57 are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned agent at (212) 527-7634. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

Respectfully submitted,

Dated: February 19, 2002

Irina E. Vainberg, Ph.D.
Reg. No. 48,008
Agent for Applicant(s)

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Vincent J. KIDD et al.

Serial No.:	09/477,082	Group Art Unit:	1642
Filed:	December 30, 1999	Examiner:	Jennifer Hunt

For: TUMOR SUPPRESSOR PROTEIN INVOLVED IN DEATH SIGNALING, AND DIAGNOSTICS, THERAPEUTICS, AND SCREENING BASED ON THIS PROTEIN

MARK-UP FOR AMENDMENT OF FEBRUARY 19, 2002

Pursuant to 37 C.F.R. §1.121, Applicants provide the following mark-up copy of the amendments requested for the claims in the above-referenced application. This document is submitted simultaneously with an Amendment and Response to the Office Action mailed on October 24, 2001.

CLAIMS:

1. Canceled

2. (Amended) The method according to claim [1] 48, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is detected by detecting the absence of a CASP8 protein in a sample from a cell.

3. (Unchanged) The method according to claim 2, wherein the absence of a CASP8 protein is detected by a method selected from the group consisting of immunoassay and biochemical assay.

4. (Amended) The method according to claim [1] 48, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is methylation of *CASP8* promoter.

5. (Unchanged) The method according to claim 4, wherein methylation of the *CASP8* promoter is detected by methylation polymerase chain reaction (PCR) assay.

6. (Amended) The method according to claim [1] 48, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is a mutation in the *CASP8* genomic gene.

7. (Unchanged) The method according to claim 6, wherein the mutation is selected from the group consisting of an insertion in the gene, a deletion of the gene, a truncation of the gene, a nonsense mutation, a frameshift mutation, a splice-site mutation, and a missense mutation.

8. (Unchanged) The method according to claim 6, wherein the mutation is a deletion in the *CASP8* gene.

9. (Unchanged) The method according to claim 8, wherein deletion of the *CASP8* gene is detected with a labeled nucleic acid probe.

10. Canceled

11. (Amended) The method according to claim [10] 51, wherein the cancer is a tumor in which a *myc* gene is amplified.

12. (Amended) The method according to claim [10] 51, wherein the cancer is a neuroblastoma.

13. (Amended) The method according to claim [10] 51, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is detected by detecting the absence of a CASP8 protein in a sample from a cell.

14. (Unchanged) The method according to claim 13, wherein the absence of a CASP8 protein is detected by a method selected from the group consisting of immunoassay and biochemical assay.

15. (Amended) The method according to claim [10] 51, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is methylation of *CASP8* promoter.

16. (Unchanged) The method according to claim 15, wherein methylation of the *CASP8* promoter is detected by methylation polymerase chain reaction (PCR) assay.

17. (Amended) The method according to claim [10] 51, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is a mutation in the *CASP8* genomic gene.

18. (Unchanged) The method according to claim 17, wherein the mutation is selected from the group consisting of an insertion in the gene, a deletion of the gene, a truncation of the gene, a nonsense mutation, a frameshift mutation, a splice-site mutation, and a missense mutation.

19. (Unchanged) The method according to claim 17, wherein the mutation is a deletion in the *CASP8* gene.

20. (Unchanged) The method according to claim 19, wherein deletion of the *CASP8* gene is detected with a labeled nucleic acid probe.

26. Canceled

27. (Amended) The kit of claim [26] 55, wherein the detection assay is an immunoassay.

28. (Amended) The kit of claim [26] 55, wherein the detection assay comprises oligonucleotide PCR primers for amplification of at least a part of *CASP8* genomic DNA.

29. (Amended) The kit of claim [26] 55, wherein the detection assay comprises a labeled oligonucleotide of at least 15 bases that specifically hybridizes to *CASP8* genomic DNA.

48. (New) A method for detecting inactivation of a *CASP8* gene, comprising detecting a modification of genomic DNA comprising the *CASP8* gene, wherein such a modification results in the absence of expression of at least one *CASP8* allele and reduction in the total level of expression of CASP8 protein to below that necessary for proper cellular regulation.

49. (New) The method according to claim 48, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is detected by detecting the absence of a *CASP8* mRNA in a sample from a cell.

50. (New) The method according to claim 49, wherein *CASP8* mRNA is detected by a method selected from the group consisting of Northern blotting and reverse transcriptase-polymerase chain reaction (RT-PCR) assay.

51. (New) A method for diagnosis or prognosis of a cancer comprising detecting inactivation of a *CASP8* gene, wherein inactivation of the *CASP8* gene results in the absence of

expression of at least one *CASP8* allele and reduction in the total level of expression of CASP8 protein to below that necessary for proper cellular regulation, and is indicative of the presence of a cancer or a poor prognosis for outcome of treatment of the cancer by conventional therapies.

52. (New) The method according to claim 51, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is detected by detecting the absence of a *CASP8* mRNA in a sample from a cell.

53. (New) The method according to claim 52, wherein *CASP8* mRNA is detected by a method selected from the group consisting of Northern blotting and reverse transcriptase-polymerase chain reaction (RT-PCR) assay.

54. (New) The method according to claim 51, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is selected from the group consisting of homozygous deletion, heterozygous deletion coupled with gene silencing by methylation, and homozygous gene silencing by methylation.

55. (New) A kit for detecting inactivation of a *CASP8* gene comprising an assay for detecting a modification of genomic DNA comprising the *CASP8* gene, wherein such a modification results in the absence of expression of at least one *CASP8* allele and reduction in the total level of expression of CASP8 protein to below that necessary for proper cellular regulation.

56. (New) A method for detecting inactivation of a *CASP8* gene, comprising detecting a methylation of genomic DNA comprising the *CASP8* gene promoter.

57. (New) The method according to claim 56, wherein methylation of the *CASP8* promoter is detected by methylation polymerase chain reaction (PCR) assay.

Respectfully submitted,

Dated: February 19, 2002

Irina E. Vainberg, Ph.D.
Reg. No. 48,008
Agent for Applicant(s)

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700

IEV: